INTERVIEW TRANSCRIPT

DISCUSSIONS WITH WORLD-LEADING EXPERTS

CGRP, PACAP & Beyond: The Future of Migraine Relief

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Introduction (00:04): For many people with migraine, it can feel like new treatments don't come fast enough. But behind the scenes, science is moving at a remarkable pace, uncovering new targets, new mechanisms, and new hope for those still searching for relief. Today, we're joined by one of the world's leading migraine researchers, Dr. Messoud Ashina, director of the Human Migraine Research Unit in Copenhagen. His groundbreaking work has reshaped what we know about how migraine starts and how to stop it. Together, we'll explore what's next in the migraine treatment pipeline, from the latest drug targets to the breakthroughs that could redefine care in the years ahead. Dr. Ashina, welcome back to the Migraine World Summit.

Dr. Ashina (00:55): Thank you. Thank you for inviting me.

Lisa Horwitz (00:56): I think this is going to be one of our most popular topics because who doesn't want more treatment options? So we have a lot of questions for you today. The first: CGRP medications have been game changers for many people with migraine. What's been the biggest impact of these medicines so far?

Dr. Ashina (01:19): Those medications are the game changer because what we are experiencing right now is something completely new. We have migraine-specific medications. We have preventive medications working on specific migraine mechanisms and the anti-CGRP pathway mechanism. After the triptans, migraine-specific acute medications, which we use to treat attacks to stop — to abort attacks — we didn't have any specific preventive medications.

Dr. Ashina (01:54): We used nonspecific medications with a varying degree of success — some of them working in some patients, some of them not working. But one of the major problems of those medications was poor adherence and poor persistence, plus side effects. And side effects, adherence, and persistence, they go together.

Dr. Ashina (02:19): So that's why when we introduced the new medications, we had a completely new arsenal of medications that we can offer our patients without all these side effects that we experienced with the old type of nonspecific medications. And it is obvious — when you develop something specific for mechanisms, the likelihood that it can cause some side effects is much, much lower. The likelihood that you have a better adherence and persistence is, of course, much, much higher.

Dr. Ashina (02:51): That's why the anti-CGRP pathway medications changed completely our clinical practice. But the problem is, Lisa, that even when we treat them and they are successful in terms of the efficacy, safety, and durability, not all patients respond to these medications. Not all patients have an optimal effect. They still have so-called residual migraines. So just one clinical example is that when you have 30 days of migraine and you drop down to 15 days — yes, it is fantastic. It's a 50% reduction, but you still have 15 days of your life spent in bed or in a bad mood and severely affected, disabled during these attacks. So that's why we need to optimize the treatment. We need also to provide patients with new drug targets, not CGRP-related targets, which can be also used in clinical practice.

Lisa Horwitz (03:51): So you find that patients adhere better to how to take the CGRPs. Do you think that's because they were specifically designed for migraine? I know it can be confusing for a patient like me to say, "Why am I taking a seizure medicine? I don't have seizures."

Dr. Ashina (04:07): Yeah, but if we're going back to the history of headache medicine, we see a lot of nonspecific medications that we used, and they were quite effective. We can't deny that they were effective. I mean, we had blood pressure medications. We have antiepileptic medications primarily used in clinical practice. At that time, we discovered them by accident.

Dr. Ashina (04:32): Those people who suffered from epilepsy or those people who suffered from high blood pressure, they were taking these medications, and they were experiencing also less migraine attacks. And later, our colleagues started investigating these medications in people without epilepsy, without high blood pressure. And they showed that compared to placebo — in the clinical trials we use placebo — they showed that they were efficacious and relatively well tolerated.

Dr. Ashina (05:03): But then in the real world, we start seeing the patients, and we experienced also some other things like adherence and persistence problems, because the patients will come back and say, "Well, it worked very well for six months or eight months, and I stopped because it stopped working," or they experienced some side effects which were totally unacceptable for patients to continue. So our discontinuation rate with these old-style medications was much, much higher.

Dr. Ashina (05:35): But we used them, and they are still using them — our colleagues and patients — and some of them are actually happy using them. And we have to remember also, Lisa, that the world is huge, and [not everyone in the world will] have access to these new medications. A lot of people around the world don't have the same access to these medications.

Dr. Ashina (06:00): And that's why it's important to emphasize that those medications are still very important players in our clinical practice, and our colleagues should continue using them and helping a lot of people with migraine around the world. We are so fortunate in the developed world or in the rich countries — in Europe, in North America — that we have this access, and we hope that this access can expand in the future also for other countries. Because with these new medications, as I mentioned before, we do see much better adherence, much better persistence, and less side effects and less problems with tolerability.

Lisa Horwitz (06:41): What percentage of people respond well to CGRPs, and what do we know about people who don't?

Dr. Ashina (06:46): Not everybody is a responder for the anti-CGRP pathway medications. In clinical trials, roughly, we see something like between 50%, sometimes 60% of people who experience at least 50% reduction in monthly migraine days. But this 50% reduction, as I mentioned before, could be down from 30 down to 15 days, or from eight days to four days.

Dr. Ashina (07:15): So the migraine spectrum is from four to eight days, relatively low frequency, up to the high frequency or constant, persistent head pain and multiple migraine attacks. OK? So there we see in clinical trials, even those who are — we call them "difficult-to-treat" patients — they respond. So approximately, I would say, between 50% to 60% of people.

Dr. Ashina (07:42): In clinical practice, where nothing is like a placebo-controlled status, we see a higher response. We see something like 70% response. But again, it all depends in which clinical practice we are. If we are in the tertiary centers, highly specialized centers, with very aggressive migraine in most of our patients in terms of intensity, in terms of duration and frequency, we do see a little bit less response — I would say between 50% and 60%, like in clinical trials. And still, a number of people are not really responding.

Dr. Ashina (08:26): And even of those who respond, as I said, not everybody is going down to the level that they can say, “Well, it’s optimal, you know — I’ve had very few attacks.” So there are still some residual attacks. There is much room for improvement, an unmet need to improve the situation.

Lisa Horwitz (08:46): Hearing you say all that, I realize I'm a problem patient. I'm your difficult-to-treat patient. Is it common for people — when I started CGRPs, I didn't experience a huge reduction in attack days, but I did experience an extreme reduction in pain and debilitation. Is this common?

Dr. Ashina (09:09): Yes, Lisa. When we teach our students and our junior doctors, we usually say the aim of the preventive medications — when we do the prophylactic, we give the preventive medications to people with migraine — it's not only reducing the frequency, it is also reducing intensity and also duration of attacks. So it's kind of a multiple effect. And I would say the three outcome measures are very, very important.

Dr. Ashina (09:37): In fact, some of the trials looked at the endpoint called "days with moderate to severe intensity," and they showed that there is also reduction of those days in patients who respond to these anti-CGRP pathway medications. That was the case with monoclonal antibodies, suggesting that it's not only working on the frequency, but it's also working on intensity. This is exactly what you experienced.

Dr. Ashina (10:04): So that's why when patients come to my office and I assess the efficacy of anti-CGRP medications, it's not only migraine days, but also days at baseline moderate to severe and how the medication changed that over the course of the treatment of at least three months.

Lisa Horwitz (10:22): I think that's a good reminder for everyone looking for an effective preventative treatment, that there are other signs a medication is working beyond just the reduction in days. So maybe don't give up so soon or cut yourself a little bit of slack because there can be progress. Lastly upon this portion of our interview, are there any biological clues that can help determine who will respond to CGRPs? Or you just have to try it to figure out if it's going to work for you?

Dr. Ashina (10:56): This question has been around for many years. Can we have some kind of biomarkers or predictors of treatment response?

Lisa Horwitz (11:05): Right, we just want it to be like a COVID test. Can I swab my nose and you tell me if it works or not?

Dr. Ashina (11:10): Well, for now, it is a utopia, I would say. Many companies, when they presented the data of efficacy of anti-CGRP pathway medications, they tried to look whether there were any signs, anything in the patient's so-called phenotype — the different symptoms. Some of them have a one-sided headache. Some of them experience nausea. Some of them more phonophobia or photophobia.

Dr. Ashina (11:41): They looked at everything, and they couldn't find anything which can predict the effect of the medication. And in fact, even if you find something, you will always find something on the big population basis. This means that even if I find something suggesting something, I cannot deny you treatment because you are not in this population, if you understand what I mean.

Dr. Ashina (12:05): So if somebody suggests that, let's say laterality — you know, unilateral headache, they can predict a better response — and you come to me and you have absolutely 100% migraine, but your migraines are bilateral, I would say, "You know what, Lisa, I deny — I'm not going to give you a drug because you have a bilateral headache," because some of the studies showed that in the big population studies there are some signals there.

Dr. Ashina (12:15): So my point is that it is perfectly well to study that and to try to address this question. But right now, a robust biomarker to predict the efficacy of these medications is absent. So the best marker, in my opinion, is my patient coming to me and complaining of migraine. And I'm a happy doctor to provide them with the medications with a 50% or 60% chance that they will respond. Isn't it fantastic?

Lisa Horwitz (13:02): It is fantastic. And it's such a good reminder that maybe by having a test, your insurance can say, "Oh, you don't fall within the lines of what says who will respond well to this med, so we can't give it to you," or your doctor won't give it to you because you don't fall in that little box

of a test that doesn't even exist yet. I'm really glad that you brought that up because I totally didn't think about that at all. So moving towards the future and away from CGRPs and what's next.

Lisa Horwitz (13:26): Your team has identified several new molecules — I think we call it PACAP [pituitary adenylate cyclase-activating polypeptide], adrenomedullin, and amylin — that can trigger migraine attacks. How might future treatments blocking these differ from CGRP inhibitors?

Dr. Ashina (13:48): Well, migraine science is fascinating because it's quite complex. The more you learn, the more you don't understand anything that's going on in people's migraine brain, what's happening during these severe migraine attacks.

Dr. Ashina (14:06): What we know is that the fundamental feature of migraine is that it can be triggered by various external and internal factors. Some of the internal factors that people with migraine quite often complain of is a cycle-related migraine. It is an internal fact. We don't know exactly the mechanisms of this trigger, but this is a fact. We see that in clinical practice. External factors could be red wine — of course, except Californian wine never induces migraine.

Dr. Ashina (14:40): But if we put it aside, we can say that it's one of the reproducible triggers of migraine attacks. So using this feature of migraine that it is provocable, but it's also treatable, we use this in our experimental setup to study the different molecules that might induce migraine attacks. How we come to this idea is that those molecules are very important and they are widely distributed in all so-called migraine anatomical structures. We call it the trigeminovascular system.

Dr. Ashina (15:17): So it's a system consisting of the blood vessels, the trigeminal nerve, which is responsible for our pain sensation, and the brain. And we know that those molecules are expressed and their receptors are also expressed there. The molecules go around and they bind to these receptors and by binding to these receptors, they activate the system. How exactly it happens in normal circumstances in people with migraine, we don't know exactly.

Dr. Ashina (15:45): But in an experimental setup, we can use these molecules by giving them either orally or intravenously, like an infusion, to study their migraine triggering. You might say, "Well, it is not good, you're triggering migraine attacks." Well, you can trigger migraine attacks with red wine. You can also trigger migraine attacks in the lab condition, but it is treatable. We can also treat that.

Dr. Ashina (16:12): Almost 80% of patients in Denmark will say, "Yes, we are going to do that because it's important for you to understand the migraine. You're helping me. You are helping my fellow patients that are suffering from migraine. And you also will help my children because I know that there is a high risk that it can also go to my kids. They will also experience that." So better understanding of migraine, better treatment.

Dr. Ashina (16:38): If we identify the molecule A inducing migraine attacks, we might develop molecule B inhibiting or stopping this molecule, either the molecule itself or binding to its receptor — the door that they [molecule A] try to open — so we can block the door by the new medication. So this way we explored and identified a series of different molecules that might be involved in migraine genesis — how the attack starts. And one of them is PACAP. It is different from CGRP.

Dr. Ashina (16:12): Just imagine that CGRP is of one family and PACAP is of another family. And this family of peptides or proteins or molecules, they can bind to different receptors, not the same receptors. So now we know that CGRP can provoke migraine attacks — this has been studied. And multiple studies are quite reproducible that it can induce migraine attacks in up to 70% of people. And we know that by blocking CGRP or its receptor, we can treat migraine attacks.

Dr. Ashina (17:50): OK, but CGRP is not alone in this family. CGRP has also some siblings: amylin and adrenomedullin. Some of them cross in a way that they can share the doors, the receptors. But some of them, no, they have their own doors.

Dr. Ashina (18:12): So we gave adrenomedullin and amylin to people with migraine and we provoked migraine attacks, suggesting that those molecules can also be involved in generating migraine attacks. And thereby we can speculate that medications working on those molecules can be efficacious as new drug targets for migraine prevention or acute treatment. So this is amylin and adrenomedullin. I also mentioned another family: it's the PACAP family.

Dr. Ashina (18:47): In this family, we have two peptides being studied in migraine. One is PACAP, pituitary adenylate cyclase-activating polypeptide. It's five letters: PACAP. And another one is VIP, but it's not because it is an important person. It is vasoactive intestinal polypeptide. So these two peptides — they are also siblings, like I told you before about CGRP, amylin and adrenomedullin. And they have their own receptors, their own doors they go and open. When we give these molecules to people with migraine, we can actually induce migraine attacks.

Dr. Ashina (19:29): And PACAP is specifically studied in terms of … let's say, it has some similarities with CGRP because it's a very strong vasodilator. So it dilates the vessels, the cranial vessels in the cranial region. And it's similar to CGRP; early studies we published back in 2009 show that it induces migraine attacks. So it was quite early in terms of suggesting it as a target. And therefore, Pharma started studying this peptide.

Dr. Ashina (18:03): Eventually, one of these pharmaceutical companies developed a monoclonal antibody against its receptor and later against the PACAP itself. It's like in the CGRP field — we have erenumab [Aimovig] acting on the receptor as a monoclonal antibody. And we have, let's say, fremanezumab [Ajovy] acting on the molecule itself. So the same — [it] was first on the receptor — one specific receptor — but unfortunately this trial failed, didn't show an effect.

Dr. Ashina (20:39): But later on, the study was conducted with a monoclonal antibody against the PACAP, against the molecule. So the molecule will be blocked and prevented from binding to this door, to open the receptor. And we showed that if you give it to just people without any history of migraine, and you provoke a little, mild headache and also very strong dilation of the vessels in the cranial region, you can in fact, completely block this response — the vessel response — and you can reduce the head pain.

Dr. Ashina (21:19): With this study, we went to another study we published last year, a so-called proof-of-concept study, in which an anti-PACAP medication — a monoclonal antibody was tested in people with migraine, in episodic and chronic — the whole spectrum — including in people who failed at least two medications before, max four, so difficult-to-treat people, the whole spectrum with migraine. And we showed in this study that it had some effect.

Dr. Ashina (21:52): But this is a small study, the first step. Now the Phase 2B study is ongoing, and hopefully, if it's still positive, we will move to Phase 3, and maybe in two or three years we have another medication, which is a completely different class of medication. What will follow after the anti-PACAP medications, we don't know. It all depends on the interest from Pharma, from industry, to develop the new drug targets.

Dr. Ashina (22:19): And when they ask me, as an expert in this field, "Do we have any need for new medications? I mean, we have now anti-CGRP pathway medications. Didn't we solve the whole problem of migraine?" And my answer is, "No, we didn't. We still have an unmet need for new medications, so please keep going and look at this literature, look at our studies." There is, of course, no guarantee that those targets we suggested will work, but at least we can try, and if we're successful,

we can expand our armamentarium of medications to our patients, and we can do much more for people with migraine around the world.

Lisa Horwitz (23:08): I'm speechless because you covered so many great points in your response, and I want to make sure that our audience caught all of them. So, currently, how you're studying new breakthroughs in migraine medicine is you get volunteers, and you inject them with some sort of molecule or antagonist that you know or that you think will trigger an attack. And then you can study in real time what is happening in a migraine body, and that leads to new discoveries and possibly new treatments down the road. That's such a simplified version of what you've said.

Dr. Ashina (23:47): Yeah, yeah. This is beautifully put, exactly. And this is what is fascinating about migraine, that you can do that. Because — can you imagine that we can provoke [in order] to study Parkinson's or to study multiple sclerosis? That would be impossible. But in migraine, we have this advantage because it is self-limiting, right? It is treatable. So, we can actually provoke. You only need volunteers — only, only — we have fantastic, brave patients coming and saying that, "Well, we are ready to sacrifice for science," basically. And they know that, of course, it's not dangerous because it's natural-occurring molecules that they have in their body. But, of course, during this experimental setup, we are infusing a higher concentration of these molecules than they'd usually expect. I can give you one example: One of the robust triggers of migraine attacks — it is a widely used medication for a different thing.

Lisa Horwitz (24:50): Really?

Dr. Ashina (24:51): If I take people with migraine, and I will give them — let's say, 20 people or 50 people, 100 people. And if I give them just a tablet of Viagra in a double-blind study, so they will come twice in a very random order, OK? And they will receive either placebo — the tablet with nothing — or they will receive Viagra. And if I do a randomization, and they come back, and I collect the diaries, 80% of them will report migraine attacks.

Lisa Horwitz (25:23): In any of your provocation studies, do you test these molecules or drugs on people who don't have headache or migraine to see if it triggers attacks on them as well?

Dr. Ashina (25:33): So, this is the beauty of these experimental models, Lisa. Now, I'm getting more and more excited, right? So, if you take 100 people without any history of migraine, no family history of migraine, and 100 people with migraine, a clear-cut migraine diagnosis. If you give the same drugs or the same substances to these 100 people, almost all of them will report some kind of head pain — very transient, one hour, and it will go away, not even needing treatment, not even needing a Tylenol, acetaminophen, nothing. And they also get immediate dilation of the vessels, because all of them are dilating the vessels, all these substances, and that's it.

Dr. Ashina (26:23): But those 100 with a history of migraine, with a diagnosis of migraine, almost 80% of them will go on and develop migraine attacks. So, why do people without migraine genetics, without a migraine diagnosis, only have transient, very mild head pain and it goes away, and in people with migraine, it evolves to a full-blown migraine attack? This is the main question in science that we have: What really starts it, how it starts, how it evolves — and another fascinating question, why it stops.

Lisa Horwitz (27:10): So, we know that CGRP and gepants affect one group of pain fibers, and Botox affects a different group of pain fibers. Can you explain in simple terms what these different pathways mean for treatment?

Dr. Ashina (27:27): We have to remember that when we talk about the pain fibers, we have to ask the question: Where are those pain fibers located in the cranial region? The brain itself, Lisa, it's indolent, OK? I mean, there is no pain sensation in the brain. The structure surrounding the brain, particularly

this so-called dura — which is meninges, we call it also; it's a plastic bag surrounding the brain, a very thin one, which protects you — and if there is infection in this particular compartment, it can cause a very serious condition called meningitis. I don't know if you heard about meningitis. It's a dangerous condition, and guess what? When people get meningitis, they complain of what? They complain of head pain; they complain of sensitivity to light, increased sensitivity for light; increased sensitivity for sound; nausea, sometimes vomiting; all the symptoms.

Lisa Horwitz (28:30): Very familiar. I'm very familiar with these.

Dr. Ashina (28:34): Yes, yes. And it could be viral meningitis; it could be bacterial meningitis. So, my point is that these pain fibers are specifically in this region and also surrounding our vessels. Now, how this vessel signaling transforms into pain signaling — this is a main question that I have in my scientific work. And what we know is that these pain fibers — there are two types of pain fibers: one transmitting slowly and one transmitting fast.

Dr. Ashina (29:07): Some of them are responsible for more tonic pain — dull pain, some of them sharp pain, but they are kind of involved in the migraine mechanisms. And some of our colleagues, they used preclinical models in animals to study these fibers, to study their responses to the different stimuli that apply in this region, and they used different drugs to see which drug affects which type of fiber.

Dr. Ashina (29:46): And some of the experiments conducted in Boston, in professor Rami Burstein's lab, they showed that apparently these medications that work like anti-CGRP medications, they work on one particular so-called A-delta fibers; and another medication used in clinical practice to actually prevent migraine attacks, Botox or onabotulinumtoxinA, it works on the C-fibers.

Dr. Ashina (30:15): So, but we have — with all respect for this very solid preclinical status — we have to remember that in clinical practice, when we start talking to patients, it could be a huge variation there in terms of efficacy of one, efficacy of another one. And the idea is that also, with this rationale, it suggests that maybe combination treatments can also be an option. Well, it's very plausible. But for the combination treatment to be better than one treatment, you need to conduct a proper randomized study to show this effect. Because otherwise, we can keep treating people with different combinations without any good proof that these different combinations are, in fact, effective compared to the one medication.

Lisa Horwitz (31:13): So, when you say combination, do you mean taking two different meds and combining them, calling them a new name, and delivering it as one pill or one injection? Or do you mean layering treatments, like I take a CGRP, but I also take Botox?

Dr. Ashina (31:32): So, just imagine that you come to my office and you complain of migraine, I diagnose migraine, clear-cut migraine, and you haven't tried anti-CGRP medication. So, I use one of the monoclonal antibodies against CGRP, and I give you this medication, and I tell you, “Come back in three months.” So, you drop from — let's say, 25 days to 15 days, OK? You come back, you say, "Doctor, I'm really happy — 10 days less, but I still have 15 days.” OK. Then what should I do?

Dr. Ashina (32:13): If I start advocating the combination treatment, it is going to be just maybe on my clinical experience, but not because I have a good status showing that the combination with something — could be with Botox, it could be another medication — would be a good option for you. Then, I'm a very good and friendly doctor, and I say, "Listen, Lisa, I think we should add another medication.” It could be, let's say, Botox.

Dr. Ashina (32:42): And you say to me, "Doctor, what would be a response that I would ideally see?" I would say, “My dream would be that I can 50% reduce that — you drop from 15 to, let's say, seven days.” You come back in three months — even after six months, let's say. I give you two cycles of

Botox medication, and you come back, and then you show me the calendar, and you say, "Yes, 30%." OK, not optimal. So, you drop from 15 to 10. Now what?

Dr. Ashina (33:22): You still feel that you have an effect, and you want to continue, but you want more. Shall I add another one? The third one? Shall I add the fourth one? Shall I add the fifth one? And how can we continue doing that? You understand what I mean? With all respect for patients, Lisa, with all respect for patients — because they're desperate, they want something that they can get rid of that, or they can call it the super optimal control — let's say, less than four days or two days maximum. But as a physician, shall I just keep going, doing so? Or shall I just ask myself, is there any evidence for that?

Lisa Horwitz (34:10): Right, because you don't want to treat your patient like they're a volunteer in a migraine study. You want to treat them as someone you're trying to reduce their migraine burden.

Dr. Ashina (34:19): Exactly. And many people, as physicians, they try to do so because they try to help the patients. And in this kind of patient and physician preferences discussion, they reach this consensus, "Well, we try another one, we try another one." But I am an academic. I mean, I am at an academic institution, and I usually go after the evidence that we have from clinical trials.

Dr. Ashina (34:49): If tomorrow you come to me and say, "Well, we have two medications [which] together [are] better than one medication," that will be evidence for me. You understand what I mean? Because of clinical experience, we all have some experience. Some people will also tell me, "Messoud, I feel better when I travel to Spain from Denmark because the weather is more nice." But I cannot prescribe that, right? So the same goes for the different medications. There are some old-style medications that work. The only way that we usually do that here, at least in our clinical practice here in Denmark, we can combine the medications if there are any comorbidities — conditions that we know that can be also treated with anti-migraine medications, we can add these medications there.

Dr. Ashina (35:41): So let's say one example: if somebody suffers from high blood pressure and migraine — well, by treating the migraine, I can say, "Well, I have a very good effect of medication, but not optimal, but the high blood pressure medication is something different. It's never been studied in migraine, but I know that there is a medication that's studied in migraine, and it is efficacious — like candesartan, [according to] a recently published paper as well."

Dr. Ashina (36:07): So I can actually switch from one antihypertension medication — blood pressure medication — from one to another one with hope that I can achieve this synergy and better effect. But doing that just like that — it is perfectly OK with me if my colleagues are doing so. I am just raising the question. If you do so — if you have a trial showing that together is better than the one, then it's OK with me. But if it's not, I just raised the question. But I have, as I said, huge respect for my colleagues trying to help patients and trying to do. The only thing is that my limit goes there [is] if we're talking about opioids, which I'm completely against — any kind of combinations, I don't want them in migraine practice.

Lisa Horwitz (37:05): Are there new pain-signaling routes that are being discovered that could lead to future drugs or devices, or [do] we still think it's pretty much this A and B? Is there a C, D, E, F of pain routes?

Dr. Ashina (37:17): No, I mean, we have pharmacological treatment with different medications, and hopefully, we will have anti-PACAP medications in the future. For neuromodulation, for different types of treatment approaches, we don't have any new stuff — unless there is something that I missed in the data and the literature. But so far, we have a number of alternative treatments as well, neuromodulations — the different devices. But in many countries, they are not reimbursed, at least in Denmark, they are not reimbursed. You have to buy them yourself.

Dr. Ashina (38:08): And honestly, with the new medications that we have, with anti-CGRP medications, less and less patients are actually talking about that and asking about that because most people are happy with these new medications. But I'm not talking only about monoclonal antibodies, we're talking about the gepants for prevention. Plus also, a number of people with chronic migraine, they receive onabotulinumtoxinA, the Botox, and they are very happy. So, not so many we have who are asking specifically about the devices.

Lisa Horwitz (38:46): Is it common to have patients who are on a monoclonal antibody and Botox? Is that an effective treatment to try to hit both pain pathways in one patient? I know we kind of covered this in your last response, but…

Dr. Ashina (39:01): I mean, not common in Denmark. I wouldn't exclude that it's something happening in private practice. But at the headache clinics at the university settings, it's actually not allowed because of lack of evidence that it can work.

Lisa Horwitz (39:17): Right, because of the lack of specific research on the combination of these two therapies.

Dr. Ashina (39:21): Specific combination is — yeah, you have to show that dual therapy, two therapies, is better than monotherapy. Then it's fine. Then it will be approved — there will be no discussion about that. But I know that in many countries that my colleagues are practicing, they have a different experience. And some of these colleagues also published real-world studies on that. So, these kinds of combinations are widely used, specifically when you combine anti-CGRP and Botox.

Dr. Ashina (39:48): But as I said, no evidence derived from randomized clinical trials, only based on experience. But it is used. And some people feel that it works better when it's a combination. Some people also told me that some of the patients, before they started taking the monoclonal antibodies, they'd been on the Botox treatment, but after the start of monoclonal antibodies, they actually prefer to stop with the Botox, not to continue with the Botox, because they feel that monoclonal antibodies are much better. Some of the people, in fact, said, "I want [to go] back to Botox. I don't want a monoclonal antibody."

Lisa Horwitz (40:36): But like so much of migraine treatment, it is a bit of trial and error because each patient is so different and will experience the medication so differently.

Dr. Ashina (40:45): Exactly. It's individual responses, yeah.

Lisa Horwitz (40:48): Which new migraine treatments are now in advanced clinical trials?

Dr. Ashina (40:54): Anti-PACAP, I would say — yeah, it all depends on what you call advanced. As I said, it's Phase 2b. And if 2b is successful, then there will be a Phase 3. And then in two or three years, we will have a new class of medication. This is at least what we know. Another is also a PAR2 [protease-activated receptor 2] antagonist or antibodies against one specific receptor. Those are also now testing. It is a Phase 2 status, so it's a proof-of-concept status.

Dr. Ashina (41:31): And if it's also successful, it would also lead to the next stage, 2b and Phase 3 status. This is a different receptor antibody — a receptor specifically also dealing with the pain sensation in this trigeminovascular system.

Lisa Horwitz (41:48): How close are we to identifying biomarkers or genetic markers that can guide therapy choices?

Dr. Ashina (41:56): Just one analogy: Just imagine that I do a study. I do the study and I take 500 people with migraine, and I measure something in their blood. And I hope that I can show the

difference between those who have migraine and those who do not have migraine. Let's imagine for a while, I find that the plasma levels — the levels in the blood of substance; well let's call it A — is elevated compared to people without migraine. Now, Lisa, when I look at the data, usually there is a huge spread of these levels. And what I compare is a statistical difference between the two groups. Now, some of them will be elevated and some of them will not be elevated at the same level as people without migraine. So based on that, I cannot diagnose you. If I do so, it would mean that you come to me and I take your saliva, I measure something in your saliva, and I tell you, "Lisa, you know what? You don't have a migraine because this level of A is normal in your saliva. So go home. This is not a migraine."

Dr. Ashina (43:20): So based on that, we can understand the migraine mechanism, speculate about that, but we cannot diagnose. Now, just imagine that I take the same sample and after that I give them a drug. And I will show that those who had higher levels had a better response — but again, in this huge spread and population-based study. And then you come to me and I measure and I found that this level of A is lower. I would say, "You know what? I know that you are not going to respond to this medication because you are there." That would be ridiculous. And I will, of course, treat you with this medication.

Dr. Ashina (44:04): I can give you one example. We took people with migraine — almost 150 people, and we gave them intravenous infusion of CGRP. And in almost 70% of them, we induced migraine attacks. And 30% didn't have migraine attacks. And then the idea was that those who are responders, hypersensitive — they reacted with a migraine attack. Those would be responders for the anti-CGRP monoclonal antibodies treatment. And those who are in that 30% are, in fact, are the 30% who are usually in the clinical trials not responding. And guess what? Those 70% of people who were sensitive to CGRP infusion, they developed the reported migraine attacks, 50% to 60% of them responded. And when we took the 30% with no migraine attacks from CGRP, and guess what? Almost 60% of them also respond. So, this hypersensitivity meant nothing.

Lisa Horwitz (45:17): Yeah. So, as much as we want to imagine a world where you could take a drop of our blood and say, "Lisa, your perfect combination of medicine is this, this, this, and this, and you'll be migraine-free for the rest of your life," we're not there.

Dr. Ashina (45:33): We're not there. I mean, it's a fascinating topic, and it's interesting to study all these substances — measuring in the saliva, in the blood, in the different compartments. Nothing wrong about that. It's interesting in terms of studying migraine mechanisms and to understand the migraine. But translating that into clinical practice — by taking the sample, predicting the effect, combination, whatever — we're not there.

Dr. Ashina (45:58): And genetics are much more complex because the migraine is not a one-gene disease, at least the common type of migraine. It's multifactorial. It's polygenic. And that's why we don't have a single one that we can use to predict anything. So, the best thing that we can do now — and we are very fortunate, and we have to be very happy about that — we have our classification.

Dr. Ashina (46:23): And using the classification, we can diagnose migraine the same way in the U.S., in Denmark, in China, in Africa, Australia, in Latin America — everywhere, and we can offer them what we have now. This is fantastic that we have this. So, this is the best biomarker, I would say, that you have. So, not denying the people based on something — on a test or something — but just saying that, "You have a diagnosis, you have a chance — let's say, at least 50% to 60% to respond. Try that. Effective, fine. Not effective, maybe we should wait longer. Not effective, we should search for other medications."

Lisa Horwitz (47:10): Yeah. It can be frustrating because we know it can often take trial and error of quite a few medications before you find one effective for you. So, I understand the hope and the dream of patients to wish there was just an easy switch to say, "This will work for you based on your

genetics," but we have to wait a little bit longer, everyone. We have to wait a little bit longer. For those who are watching today and they're waiting for that next big breakthrough, what would you say to them to stay hopeful and engaged in their care plan?

Dr. Ashina (47:43): In spite of this great access that we have — at least in our part of the world — we still have many people underdiagnosed and undertreated. So, this is important because we need patients, we need people with migraine engaged in this process to actually go and seek actively, proactively for help because there are a lot of opportunities now.

Dr. Ashina (48:09): We have these good medications — OK, not working in everybody, but still very good, efficacious, well tolerated new medications for prevention — and we should use that. Can you believe that 30 years passed since we introduced the triptans, we still have people who never tried triptans? We still have people who tried only one triptan. Even when we know that the one triptan trial is not sufficient. You need to try two, three triptans until you find the right one individual for you.

Dr. Ashina (48:46): We're still talking about that. So, that's why we're talking about a very simple thing. We're talking about this awareness among the people with migraine. There is still this problem — stigma around migraine and remembering also that we are not the only ones in this world. We have a huge population outside of our world totally underdiagnosed, totally undertreated in many places around the world.

Lisa Horwitz (49:16): And I think a lot of these people are undiagnosed and undertreated because this does have some genetic component. Maybe they had a grandparent or a parent who had headache or migraine in the ‘50s, ‘60s, ‘70s when we didn't have these treatments that are available now. So, they think, "Well, this is just how you live." And they don't try to seek care and they don't know that there are things that can greatly improve your quality of life.

Dr. Ashina (49:42): Can you imagine that even in countries such as Denmark, where we have a lot of focus on headache and migraine and we did a lot of research in our country in this field — and we're very proud of being one of the important hubs around the world for migraine research and headache medicine. We did a survey, an internet-based survey, and we found that 25% of responders experienced at least once a week headache and never consulted a physician.

Dr. Ashina (50:13): They say something about that — maybe they just consider that so trivial, or maybe embarrassing to go to the doctor and talk about that because the doctor will say, "OK, just go and take an aspirin or take a Tylenol."

Lisa Horwitz (50:29): I was not diagnosed with migraine till I was almost 29 years old because I thought the headaches I was experiencing were what everyone else experienced when they had a "regular, traditional” headache. So, it can be hard for a person with migraine to know that their pain and their disablement is so much greater than what an average headache is. And yeah — it is kind of crazy that still in this day and age — but that's why we're here. That's why we're at the summit. That's why we're trying to get this information out so people can recognize migraine in themselves and maybe in those around them and help spread the word.

Dr. Ashina (51:06): Absolutely. This is very important and your initiative and what you're doing — it's extremely important. The only thing that we need to do, as I said before, we need to spread it around the world. We need to do more to reach out to as many people as we can.

Lisa Horwitz (51:23): Should patients consider joining a clinical trial? And if they're interested in joining one, what's the best way to find a trial that's right for them?

Dr. Ashina (51:32): Yeah — it's very different from country to country. It's extremely important that the patients participate in clinical trials because without clinical trials, we will never understand that.

One of the best things that happened in our field, Lisa, is that we have a classification, we can diagnose migraine — and it's pretty homogeneous in this context. OK? So meaning that including patients in the U.S., including patients in France, in Germany — in other countries around the world — we include the same type of patients. And by including this type, this provides us a basis to study the migraine.

Dr. Ashina (52:12): And when we do the clinical trials and we can show that the medications are working, we show that it's not working only on patients' frequency, intensity, and duration of attack, but also on the quality of life. We can actually prove that migraine is not just a headache, it's a very complex disorder or disease associated with a specific biology for this condition, which is different from other conditions.

Dr. Ashina (52:42): And specific biology — I will mystify the migraine as just a normal headache. It's just a statement that migraine is a disease with specific mechanisms. And when you have specific mechanisms, you can develop specific drugs acting on those mechanisms. And again, it's another statement, another proof that this is not simple head pain and headache. So this is extremely important.

Dr. Ashina (53:10): And when the people with migraine participate in clinical trials, they are not helping only physicians who are treating the people, or industry who are making money, of course, out of this, but they're helping themselves because they're expanding this armamentarium of medications. Expanding this armamentarium is extremely important because it's providing us with different molecules.

Dr. Ashina (53:34): And we can play around with these molecules, we can treat — we can maybe in the future, as you said — we can personalize that. This is something that can happen. It's not yet there, but the more we learn, the more we have — it's better also for the future. We're not only thinking about ourselves, but also thinking about children. I'm a migraineur myself, and I have kids with migraine. So it's important for me — but so many people are affected.

Dr. Ashina (54:01): I mean, if we go to a party, if we go anywhere, we see a lot of people. And if they find out that you are a researcher or a physician dealing with migraine, always somebody will approach you and say, "Listen, I had so much headache, and it's so bad." Or another one could come and say, "Well, I suffered from migraine [for] so many years, but now I'm getting old, it's getting a little better, but I understand why you study the migraine."

Lisa Horwitz (54:27): Where can we learn more about what you're doing and follow your work?

Dr. Ashina (54:33): The good news is that I received one of the major grants in Denmark from the Danish National Research Foundation. The Center of Excellence was inaugurated on September 1st [2025], Center for Discoveries in Migraine. We're going to have our website very soon, hopefully, and we will post all new research that we do, but usually I post that on X (formerly Twitter), or I do it also on LinkedIn. On LinkedIn, we have a lot of new stuff also we're presenting there.

Dr. Ashina (55:11): Just yesterday we had a nice post about our hypothesis, how migraine pain starts. So all these things can be found through social media — but we will have a dedicated website for that. For the people with migraine, we created a nice website under the umbrella of the National Knowledge Center for Headache Disorders, which I initiated in 2018, and it is financed by the Danish government. The aim of this organization is to provide all information for patients, for people suffering from migraine, for their relatives, but also for other stakeholders that are interested in that, but it's in Danish. There, they can also read the newsletters about everything that's going on, specifically in Denmark, but also outside of the world, if it's something of interest for patients. For the research part, we will have our website specific for that.

Lisa Horwitz (56:19): Thank you so much again for your time today, Dr. Ashina. It was an absolute pleasure.

Dr. Ashina (56:25): Thank you. Thank you for inviting me.